

ORIGINAL ARTICLE

The liver-first approach for synchronous colorectal liver metastasis: a 5-year single-centre experience

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Abstract

Background: For patients who present with synchronous colorectal carcinoma and colorectal liver metastasis (CRLM), a reversed treatment sequence in which the CRLM are resected before the primary carcinoma has been proposed (liver-first approach). The aim of the present study was to assess the feasibility and outcome of this approach for synchronous CRLM.

Methods: Between 2005 and 2010, 22 patients were planned to undergo the liver-first approach. Feasibility and outcomes were prospectively evaluated.

Results: Of the 22 patients planned to undergo the liver-first strategy, the approach was completed in 18 patients (81.8%). The main reason for treatment failure was disease progression. Patients who completed treatment and patients who deviated from the protocol had a similar location of the primary tumour, as well as comparable size, number and distribution of CRLM (all $P > 0.05$). Post-operative morbidity and mortality were 27.3% and 0% following liver resection and 44.4% and 5.6% after colorectal surgery, respectively. On an intention-to-treat-basis, overall 3-year survival was 41.1%. However, 37.5% of patients who completed the treatment had developed recurrent disease at the time of the last follow-up.

Conclusions: The liver-first approach is feasible in approximately four-fifths of patients and can be performed with peri-operative mortality and morbidity similar to the traditional treatment paradigm. Patients treated with this novel strategy derive a considerable overall-survival-benefit, although disease-recurrence-rates remain relatively high, necessitating a multidisciplinary approach.

Keyword

synchronous colorectal liver metastasis

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Introduction

Up to one-fourth of patients who present with colorectal cancer have concomitant colorectal liver metastasis (CRLM).^{1,2} Patients with these synchronous CRLM are thought to have a worse prognosis compared with patients with metachronous CRLM.³ While surgical resection of CRLM is regarded the only potential for a cure,^{4,5} the simultaneous presentation of primary and secondary disease provides a unique chance in deciding the optimal therapy sequence in these patients.

The classic approach for patients with synchronous CRLM encompasses resection of the primary tumour, followed by

optional adjuvant chemotherapy and eventually succeeded by liver surgery. Potential advantages of this approach are primary tumour oriented and include prevention of local ingrowth, bowel obstruction or bleeding from the colorectal carcinoma. However, major disadvantages include progression of the CRLM beyond resectability, especially after a delay in the treatment paradigm owing to morbidity associated with the colorectal surgery. Moreover, in case of chemotherapy, serious hepatotoxicity can occur^{6,7} or the hepatic lesions can disappear.⁸ While some authors have therefore supported a simultaneous resection of the primary tumour and concurrent liver disease,^{9–11} others advocated a staged approach in which the liver is operated on before the

primary tumour and increasingly frequently preceded by induction chemotherapy.^{12–14} Particularly for rectal primaries, the latter approach is regarded as more natural as the post-radiation required waiting period offers ample time for performance of a liver resection. Additional rationale for this reversed sequence of therapy is that CRLM are the main cause of death and that it is therefore important to eliminate these lesions first. With a liver-first approach, the treatment of the CRLM is by no means interrupted by possible complications after resection of the primary tumour. A concurrent advantage could be that administration of pre-operative chemotherapy provides a chance to evaluate a response and thereby define the tumour biology of the CRLM. Moreover this strategy provides a certain window during which possibly latently present extrahepatic metastases have a chance to declare themselves.^{15,16}

Currently, there are very little data available regarding the liver-first approach.^{12,14,17,18} Therefore, the aim of the present study was to describe the experience with the liver-first approach in a tertiary referral centre. Moreover, we sought to not only examine the feasibility and short-term outcomes after the liver-first approach, but also to assess the influence of this sequence in therapy on the oncological outcome.

Methods

Prospectively collected data on patients who underwent liver surgery from 1st January 2005 to 31st December 2010 were queried from the hepatectomy databases at a large hepatobiliary centre (Maastricht University Medical Centre). All patients with synchronous CRLM were identified. In 22 of these patients, a liver-first approach was planned and these patients are the scope of the present study.

During pre-operative assessment, patients were deemed resectable only if a resection with negative margins was expected for all known disease, both intra- and extrahepatic. Moreover, only patients in whom an adequate future liver remnant was anticipated on computed tomography (CT) volumetric analysis were considered candidates for hepatic resection.^{19,20} Furthermore, the future liver remnant had to incorporate a minimum of two adjacent segments with sufficient vascular in- and outflow and adequate biliary drainage to be regarded suitable for resection.^{5,21}

In short, after patients were diagnosed with synchronous CRLM, they were referred to our tertiary referral centre (coordinated by the Surgical Oncologic Network of Limburg) and were subsequently presented and discussed in a multi-disciplinary oncology meeting, during which their treatment strategy was established. Specifically, all patients with rectal cancer underwent standard locoregional staging with standard T2-weighted magnetic resonance imaging (MRI) which was in some cases extended with an additional gadofosveset-enhanced imaging sequence for lymph node staging, in accordance with our institutional protocol described previously.²² For patients with a primary tumour located in the colon, pre-operative staging was generally ascer-

tained using a computed tomography (CT) scan. In general, all patients who were diagnosed with a rectal tumour, based on these imaging modalities, received pre-operative radiation therapy consisting of either a short course (5×5 Gy) of radiation or a long course of 28 fractions of 1.8 Gy radiation with capecitabine (chemoradiation, i.e. chemotherapy as a radiosensitizer, capecitabine 2×1000 mg/m²), followed by pre-operative chemotherapy aimed at minimizing the likelihood of a (microscopically) positive resection margin after resection of the primary tumour, according to the national guidelines.²³ In line with our institutional chemotherapy protocol, patients receive a total of six cycles. Moreover, in our institution, patients with a locally advanced rectal carcinoma, which was defined as a T4 tumour or a T3 tumour with involved or threatened mesorectal fascia or an N2-status or a distally located T3N1 tumour, receive chemoradiation followed by two cycles of pre-operative full-strength chemotherapy (i.e. oxaliplatin, 130 mg/m² with or without bevacizumab 7.5 mg/kg). Patients with a non-locally advanced rectum carcinoma are generally treated with a short course of radiation therapy followed by three cycles of pre-operative chemotherapy (i.e. oxaliplatin, 130 mg/m² with or without bevacizumab 7.5 mg/kg). This also allowed evaluation of the tumour response to chemotherapy. The remaining cycles are generally administered either after liver resection or after completion of the resection of the primary tumour. Each deviation from this protocol only takes place after careful and thorough evaluation at our weekly, institutional multi-disciplinary meeting. Reasons for not completing all cycles of chemotherapy are mainly patient based and include too severe side-effects of pre-operative chemotherapy. However, rather than treating all patients according to a strict and rigid protocol, we intend to provide each patient with a tailor-made treatment regimen.

After initial resectability of the CRLM was assessed based on the criteria described above, all patients with a primary tumour located in the rectum were considered for the liver-first approach, whereas patients with a colorectal tumour located in the colon were selected on a case-by-case basis in order to provide a tailor-made management plan.

Data collection

Apart from standard demographic data (i.e. age and gender), the following data were also collected for each patient: characteristics of the primary tumour (i.e. location and size of the primary lesions, TNM stage) as well as of the CRLM (i.e. distribution, number and size of the lesions). Moreover, data concerning treatment-related variables were collected (i.e. peri-operative receipt of radiation and/or chemotherapy, details of the hepatic surgery as well as data regarding the operation on the primary tumour). Furthermore, data regarding post-operative outcome (i.e. presence, type and severity of in-hospital or 90-day morbidity and post-operative mortality within 90 days of treatment) and data regarding disease recurrence and vital status were noted. Disease recurrence was defined as a lesion that was a biopsy

proven recurrent adenocarcinoma or a lesion that was deemed suspicious on cross-sectional imaging in the setting of an elevated carcinoembryonic antigen (CEA) level.

Statistical analyses

All statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Summary statistics were obtained and presented as percentages or median values. Upon comparing categorical data, the χ^2 -test, or if deemed appropriate Fisher's exact test, was used, while the Mann–Whitney *U*-test was used to compare continuous data. Recurrence-free and overall survival analyses were performed using the non-parametric product limit method.²⁴ Overall, a *P*-value less than 0.05 was considered significant.

Results

Patient and tumour characteristics

Between 1st January 2005 and 31st December 2010, 186 patients underwent liver directed surgery for CRLM at our institution and were queried from our hepatobiliary database. Specifically, 90 patients presented with synchronous CRLM and in 22 of these patients (24.4%), a liver-first approach was planned during this 5-year period. These latter patients are the scope of the present study. The characteristics of these patients are detailed in Table 1. The site of the primary tumour was the rectum in most patients (*n* = 19; 86.4%), whereas three patients (13.6%) had a carcinoma located in the colon. The median pre-operative CEA level (range) was 15.8 µg/L (1.90–321.0).

At the time of presentation, 15 patients (68.2%) complained of primary tumour-associated symptoms. Furthermore, another two patients (12.5%) developed symptoms caused by the primary tumour during the course of their illness, but before their liver-directed surgery. Both of these patients developed an obstruction of the bowel as a result of their colorectal carcinoma and subsequently underwent a laparotomy during which a diverting ostomy was constructed, before their liver-directed surgery.

Details of radiation and chemotherapeutic therapy

In total, 21 patients (95.5%) received radiation therapy of their primary tumour. Eight patients (36.4%) received a short course of radiation therapy, of whom seven patients (31.8%) also received multiple cycles of pre-operative chemotherapy before surgery. Moreover, 13 patients (59.1%) underwent a long course of radiotherapy with a chemo-sensitizer (chemo-radiation therapy). Nine of these patients (40.9%) received additional cycles of pre-operative systemic chemotherapy (i.e. not as chemo-sensitizer). Furthermore, one patient (4.5%) did not receive radiation therapy of the primary tumour, but this patient did receive pre-operative chemotherapy. All of the patients who received pre-operative chemotherapy received an oxaliplatin-based chemotherapy regimen. Moreover, the majority of patients (*n* = 10) received one or more cycles including biologicals (i.e. bevacizumab).

Table 1 Patients and tumour characteristics

Variable	No. of patients (%), <i>n</i> = 22
Patient characteristics	
Median age [range], year	65 [41–86]
Sex (male)	16 (72.7)
Median pre-operative CEA level [range], µg/L	15.8 [1.90–321.0]
Primary tumour site	
Location of the primary tumour	
Colon	3 (13.6)
Rectum	19 (86.4)
Symptoms caused by the primary tumour	
Symptoms at the time of presentation	
None	7 (31.8)
Rectal blood loss	9 (40.9)
Changes in bowel habits	4 (18.2)
Bowel obstruction	3 (13.6)
Onset of symptoms during the course of the illness	
None	5 (22.7)
Bowel obstruction	2 (9.1)
AJCC T-stage on pathology ^a	
ypT1/ypT2	2 (12.5)
ypT3/ypT4	14 (87.5)
Lymph node status on pathology ^a	
ypN1/ypN2	6 (37.5)
ypN0	10 (62.5)
Hepatic metastasis	
Size of largest metastasis (median [range]), cm	1.7 [0.4–6.6]
No. of metastasis (median [range])	2 [1–7]
Location (unilobular)	10 (45.5)

^aExcluding patients who did not undergo resection of their primary colorectal tumor (*n* = 6).

Four patients (18.2%) received interval chemotherapy in the surgical window between hepatic and colorectal surgery, excluding those patients who did not undergo resection of their primary. Nine patients (40.9%) who completed the curative intent treatment plan received adjuvant chemotherapy after completion of both operations. For those patients who received chemotherapy after their liver resection (either interval of adjuvant), this generally also consisted of an oxaliplatin-based regimen.

Details of surgery

Of the 22 patients in whom a liver-first approach was planned, in one patient (4.5%) no liver resection was performed owing to a per-operative diagnosis of locoregional perihilar lymph nodal disease. These lymph nodes were located adjacent to the vena cava, making performance of a lymphadenectomy impossible. The operative characteristics of the 21 patients who did undergo a liver

Table 2 Details of surgical procedures

Variable	No. of patients (%), <i>n</i> = 22
Type of liver resection	
None	1 (4.5)
Single stage resection	
<Hemihepatectomy	11 (50.0)
Hemihepatectomy	8 (36.4)
Plus additional minor resection	4 (18.2)
Central hepatectomy	1 (4.5)
Two-stage resection	
Triple metastasectomy and subsequent hemihepatectomy	1 (4.5)
Type of colorectal resection	
None	6 (27.3)
Watchful wait	2 (9.1)
Extensive metastatic disease	4 (18.2)
Transanal endoscopic microsurgery	1 (4.5)
Low anterior resection	9 (40.9)
With diverting ostomy	6 (27.3)
Hartmann's resection	2 (9.1)
With revision ostomy	1 (4.5)
Right hemicolectomy	1 (4.5)
Rectum extirpation with end ostomy	2 (9.1)
Rectosigmoid resection with end ostomy	1 (4.5)
Median of lymph nodes harvested [range]	12 [4–14]

resection are detailed in Table 2. Importantly, one patient (4.5%) underwent a planned two-stage approach for his bilateral CRLM. This patient also underwent portal vein ligation (PVL) of the right portal vein during the first stage of his treatment.

After a median interval of 3 months (range: 1–11), 16 patients (72.7%) underwent surgery for their primary tumour. The operative characteristics of these 16 patients are detailed in Table 2. Of the five patients who did not undergo surgery of their primary tumour, three patients (13.6%) developed extensive metastatic disease and were therefore not thought to be candidates for resection. Specifically, in two of these latter patients, the extrahepatic metastases were diagnosed during attempted colorectal resection. Furthermore, in two patients (9.1%) the primary tumour had disappeared as a result of the chemo-radiation therapy and therefore in these patients a wait-and-see approach was conducted, in accordance with a watchful wait protocol currently executed at our institution. A complete response of the primary tumour was diagnosed by endoscopic examination and was pathologically confirmed by a biopsy of the region of the lesion. Altogether, the total number of patients not treated according to the protocol was four (18.2%), whereby excluding the two patients who are presently included in the follow-up protocol for complete responders to chemo-radiation. (Fig. 1)

Upon comparing patients who completed their per-protocol treatment and patients who deviated from the protocol, no differences were observed with regard to the location of the primary tumour, size and the number of CRLM or the distribution of the lesions (all $P > 0.05$). Moreover, there was no statistically significant difference in the likelihood of succeeding between patients who had a symptomatic primary lesion and patients who did not ($P = 0.63$).

Pathological characteristics

The median number of CRLM resected was 2 (range: 1–7), with a median size of the largest lesion of 1.7 cm (range: 0.4–6.6). On final pathological analysis, 20 patients (95.2%) had negative hepatic margins (R0).²⁵ Moreover, in one patient (4.8%), no viable tumour was found.

Excluding patients who did not undergo resection of their primary colorectal tumour and therefore did not have pathological staging of their primary tumour, most patients ($n = 14$; 87.5%) had a ypT3 (i.e. invasion through the muscularis propria into pericorectal tissues) or a ypT4 (i.e. direct invasion in adjacent organs or structures) primary tumour.²⁶ Six patients (37.5%) were found to have positive lymph nodes, therefore 10 patients (62.5%) had node negative disease however all in the setting of pre-operative chemotherapy (ypN0).

Post-operative and oncological outcome

The complication rate during hospital admittance after liver-directed surgery, or the 90-day post-operative period, was 27.3% ($n = 6$), all of which were major complications (Clavien grade ≥ 3).²⁷ The specifics of post-operative morbidity are detailed in Table 3. Importantly, there was no significant difference in the interval between hepatic surgery and the resection of the primary tumour when patients who did develop complications [median: 3.4 months (range: 3.3–9.8)] were compared with patients who did not [median: 2.3 months (range: 1.0–10.9)] ($P = 0.095$). Moreover, eight patients (44.4%) developed post-operative complications after (attempted) resection of their primary tumour ($n = 18$), of whom half ($n = 4$; 22.2%) had also previously developed post-operative morbidity after liver-directed surgery. While two patients (11.1%) developed minor complications (Clavien grade <3), six patients (33.3%) developed major complications (Clavien grade ≥ 3).²⁷ Importantly, one patient (5.4%) died within 90 days of operation for the primary tumour, on post-operative day 74.

At the time of last follow-up, one-third ($n = 6$; 33.3%) of the patients who underwent the complete curative paradigm or in whom a wait-and-see approach was conducted had developed recurrent disease. Specifically, none of the two patients in whom a wait-and-see approach was conducted experienced a local recurrence. The median recurrence-free survival after hepatic surgery was 14.5 months. The pattern of recurrence was combined intra- and extrahepatic recurrence in four patients (25.0%), whereas another two patients (12.5%) developed recurrent disease outside of the liver only. No patient developed recurrent disease solely in

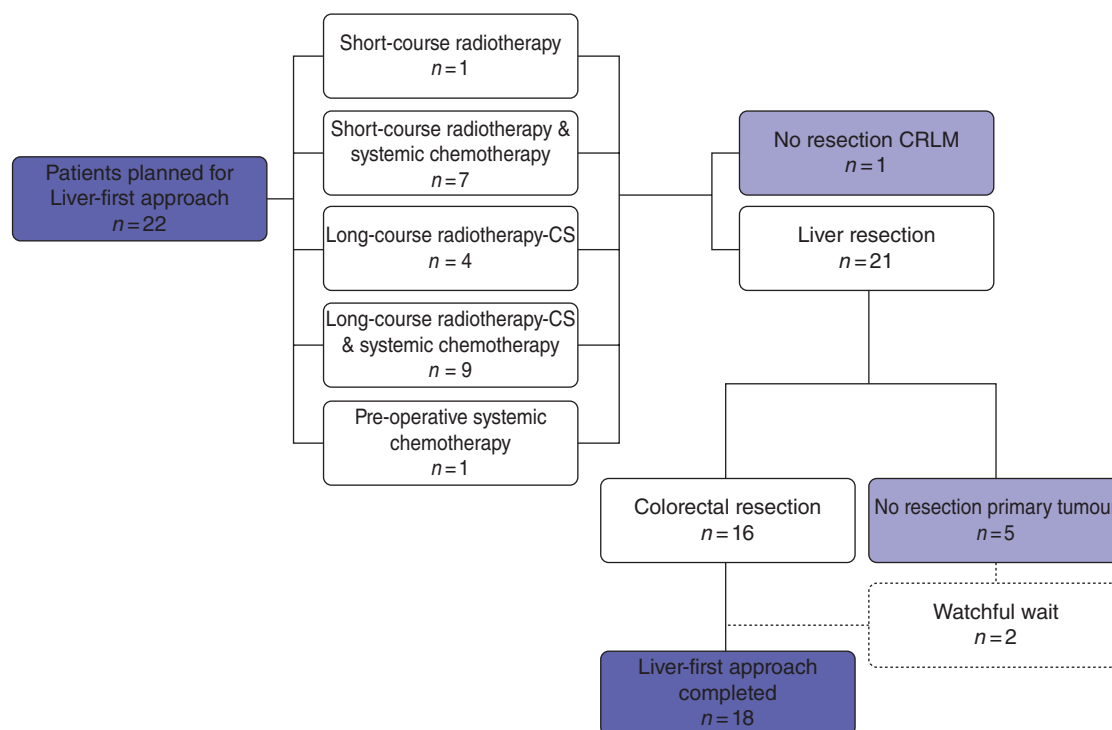


Figure 1 Flow chart of the 22 patients included in the present study. CRLM, colorectal liver metastasis; CS, chemo-sensitizer

the liver. On an intention-to-treat basis, the estimated overall 1- and 3-year survival calculated from the time of liver surgery were 74.2% and 41.1%, respectively, with a median survival of 35.5 months. (Fig. 2)

Discussion

Based on serious potential pitfalls of the traditional approach for synchronous CRLM, it has been proposed to reverse the order of the staged approach for these patients i.e. the liver-first approach. However, most data on this sequential in the treatment of patients with CRLM comes from a small series. Mortensen *et al.*²⁸ described 26 patients in whom the CRLM were resected before the primary tumour. However, in only a small portion of these patients, this therapeutic sequence was a planned strategy. Mentha *et al.*^{12,17} have reported on their experience on several occasions with the largest series including 35 patients, whereas Verhoef *et al.*¹⁸ reported on 23 patients in whom a liver-first approach was planned. Moreover, this latter group reported on a cohort of 20 patients who all completed their liver-first strategy within a larger study on patients with synchronous CRLM.²⁹ Nonetheless, in this previous study, the specific characteristics of these 20 patients were not described in great detail.

As previously mentioned, our institution has adopted the liver-first strategy several years ago, particularly in all patients who present with synchronous CRLM from a rectal origin but also in selected patients with synchronous CRLM from a primary

tumour located in the colon, when an indication for pre-operative radiation therapy or chemotherapeutic regimens is present. In the current series, we report on 22 patients who were planned to undergo a liver-first approach during the 5 years of inclusion. Specifically, 18 patients (81.8%) were treated per protocol and completed the treatment plan for liver and primary tumours. This percentage of feasibility is higher than the rate of patients who completed the formalized treatment plan reported by Verhoef *et al.* (69.6%).¹⁸ Moreover, in the most recent series by Mentha *et al.*¹² the authors report that 14% of patients did not complete the curative paradigm, while an additional 20% of patients had their primary tumour removed at the same time as the hepatic resection (i.e. a simultaneous approach). Therefore, in this previous study, merely 66% of patients were treated according to protocol. The feasibility of being able to complete the entire treatment protocol under the liver-first approach has been of some concern. As it has been stated that surgical management of CRLM is associated with an increased quality of life compared with chemotherapeutic therapy alone,³⁰ an aggressive approach seems warranted. In our cohort about one-fifth of patients were unable to complete their treatment paradigm, as four patients (18.2%) deviated from the protocol as a result of the development of extrahepatic disease during the course of their treatment (i.e. under chemotherapy). It has been shown that tumour progression of CRLM under pre-operative chemotherapy is associated with a poor outcome, even after all (visible) metastatic disease is completely removed during curative intent surgery.^{15,16} This supports

Table 3 Specifics of direct post-operative outcomes

Variable	No. of patients (%), <i>n</i> = 22
Liver-directed surgery	
Post-operative complications (any)	6 (27.3)
Minor (Clavien grade < 3)	0
Major (Clavien grade ≥ 3)	6 (27.3)
Post-operative mortality (within 90 days)	0
Specific complications	
Biloma	3 (13.6)
Intra-abdominal abscess	1 (4.5)
Iatrogenic bowel perforation	1 (4.5)
Stroke	1 (4.5)
Surgery on primary colorectal tumour ^a	
Post-operative complications (any)	8 (44.4)
Minor (Clavien grade < 3)	2 (11.1)
Major (Clavien grade ≥ 3)	6 (33.3)
Post-operative mortality (within 90 days)	1 (5.6)
Specific complications	
Intra-abdominal abscess	4 (22.2)
Anastomotic leakage	1 (5.6)
Re-bleeding	1 (5.6)
Pneumonia	2 (11.1)
Fascia dehiscence	1 (5.6)
Urinary tract infection	1 (5.6)
Surgical site infection	1 (5.6)

^aExcluding patients in whom no resection for a primary tumour was attempted (*n* = 4).

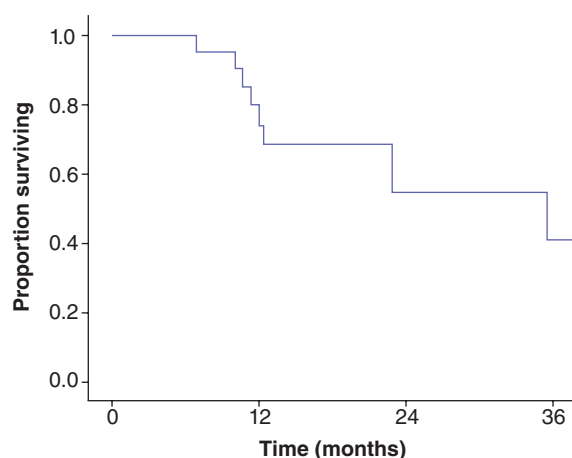


Figure 2 Kaplan-Meier curve showing overall survival of the 22 patients who were planned to undergo the liver-first approach (intention-to-treat analysis)

the potential benefit of the surgery-free interval as patients can be 'saved' an operation in the case of disease progression.

In two patients (9.1%), a complete response of the primary lesion owing to radiation therapy was observed. While the disappearance of the primary lesion has been shown to be of concern, with adequate follow-up and strict surveillance including regular evaluation of the CEA-level and appropriate cross-sectional imaging, patients can still be treated under a curative paradigm.³¹ Therefore, these patients were not classified as treatment failures in the present study. Furthermore, although obstruction by the primary tumour during the course of treatment occurred in five patients (22.7%), in all of these a diverting ostomy was constructed and in none of these patients this was a reason to divert from the planned strategy.

On another note, the potential surgical morbidity in managing patients with synchronous CRLM has also been an area of ongoing concern. Specifically, under the liver-first protocol, a complication after hepatic resection can result in a delay with regard to the treatment of the primary tumour. In our series, six patients (27.3%) developed complications after liver-directed surgery, whereas the post-operative mortality was zero. These numbers corroborate the incidence of post-operative morbidity reported in other, larger series.^{32,33} Importantly, the interval between the operations for the hepatic and primary disease was similar for patients who did and patients who did not develop complications after liver surgery. Moreover, for patients in whom a too small future remnant is anticipated and who are therefore at an increased risk of developing hepatic failure, portal vein embolization (PVE) or PVL could be undertaken to enlarge the future liver remnant by means of hypertrophy,^{34,35} especially as patients treated with the liver-first approach are generally regarded to have advanced disease and undergo several cycles of pre-operative chemotherapy which could have subsequently caused hepatocyte damage. After surgery on the primary tumour (*n* = 18), post-operative morbidity occurred in eight patient (44.4%). Notably, one patient (5.6%) died during the 90-day post-operative period. These complication rates are similar to the post-operative morbidity rates reported in cohorts of patients who had not previously undergone a liver resection.^{36,37}

Apart from the short-term results of the liver-first approach, it is important to also emphasize the influence on long-term outcomes (i.e. recurrence and survival) in these patients. In the current series, on an intention-to-treat basis, the estimated overall 1- and 3-year survival calculated from the time of liver surgery were 74.2% and 41.1%, respectively, with a median survival of 35.5 months. These statistics are corroborated by other, albeit limited, series on patients operated for synchronous CRLM, treated using the traditional approach^{3,38} or the liver-first strategy.¹² However, owing to advances in medical oncology (e.g. modern chemotherapy regimens)^{39,40} as well as surgical oncology (e.g. performance of repeat resections⁴¹ and improved peri-operative outcome),⁴² the overall survival for all patients who

present with CRLM has improved dramatically. Therefore, it has become increasingly important to assess disease recurrence in order to draw conclusions with regard to the curative potential of the proposed treatment paradigm. In the current cohort, six (33.3%) of the patients who were treated per-protocol had developed recurrent disease at the time of the last follow-up. Available data on recurrence after the liver-first approach are scarce and range from 25.0%¹⁸ to 66.7%¹² at the time of the last follow-up. However, as recurrence is associated with time passed since surgery, it is preferred to investigate this variable in a time-to-event modus rather than comparing the crude probabilities. In the present cohort, we found a median recurrence-free interval of 14.5 months. While other studies on the liver-first approach did not report a median recurrence-free interval, this interval is in concordance with those reported in assorted cohorts of patients with CRLM.^{43,44} Moreover, although the recurrence rates reported in the series on the liver-first approach varied greatly, they do show that disease recurrence is not uncommon and therefore, especially in the proposed treatment sequence, there seems to be a role for a multidisciplinary approach.

The present study has several limitations associated with the retrospective nature of the study. This limited number of patients reflects the highly selected nature of the cohort of patients with synchronous CRLM who were considered for this comparatively novel approach. As a result of the small sample size, the study has limited statistical power and therefore the statistical analyses are also limited.

In conclusion, the present study shows that resection of hepatic metastasis before resection of the primary colorectal tumour can be performed with acceptable peri-operative mortality and morbidity rates, similar to the traditional treatment paradigm for synchronous CRLM. Especially when the primary tumour requires a neo-adjuvant treatment strategy that provides a window for the liver-first approach, this sequence of therapy should be considered. Although over one-fifth of patients were not able to complete the entire treatment plan, an important finding of this series is that the anticipated pitfalls of this approach (i.e. growth of CRLM beyond resectability and bowel obstruction by the primary tumour) were not found to alter the proposed treatment strategy. Moreover, the here presented data show that patients with synchronous CRLM treated with the liver-first strategy derive a considerable overall-survival benefit, although disease-recurrence rates remain relatively high. Especially in light hereof, the selection of patients for this novel strategy should be individualized and incorporated in a multidisciplinary approach to achieve the best outcomes.

Conflicts of interest

None declared.

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